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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/692,918	10/24/2003	Frank Grosveld	CARP0015-101	9062

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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	PAPER NUMBER
1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/692,918	GROSVELD, FRANK	
	Examiner	Art Unit	
	ANOOP SINGH	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,7,8,10,11,33-36,39,41 and 42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 7-8, 10-11, 33-36, 39, 41 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment to the claims and replacement drawing filed September 29, 2008 has been received and entered. Applicants have amended claims 1, 3, 7-8, 10, while claim 2, 4-6, 9, 12-32, 37-38 have been canceled. Applicants have also added claims 41-42 generally directed to elected invention.

Claims 1, 3, 7-8, 10-11, 33-36, 39, 41 and 42 are pending in this application.

Election/Restrictions

Applicant's election with traverse of group I in the response filed dated April 27, 2006 was acknowledged. The traversal was on the grounds that Group I and Group II-III should be examined together because search for invention of Group I would be coextensive with Group II and III. In addition, applicants asserted that only method of Group I would be required to make the antibody recited in Groups II and III. Applicant's arguments for examining elected method group with the product claims were not persuasive for the reasons of record (see office action dated 2/12/2007).

Claims 1, 3, 7-8, 10-11, 33-36, 39, 41 and 42 are under consideration.

Priority

Applicants' argue that each potential method of making encompassed by the claims does not need to be specifically described or enabled. Applicants assert that enablement requirement is met if the description enables any mode of making and using the claimed invention.

Applicants' arguments have been fully considered but they are not persuasive. Contrary to applicants' assertion the construct disclosed by applicants in application GB0110029.6 filed in Great Britain on 4/24/2001 fails to provide

descriptive support for lox P site instant claims. It is noted that applicants' have extensively relied on a post filing art of Janssens et al (Proc Natl Acad Sci U S A. 2006 Oct 10;103(41):15130-5, art of record) for the enabling support that uses a specific transgenic loci that shows multiple rearrangements in a μM animal that do not produce surface IgM and have block in B cell development at a pre B cell stage. Contrary to applicants' assertion there is not adequate support or enablement for claims in the manner provided by the first paragraph of 35 U.S.C. 112 in prior filed applications to a method for producing single heavy chain antibody embraced by the breadth of the claims. Although loxP sits is not required by the claimed method, the specification fails to enable a method for producing a single chain antibody having a camelid VHH or camelised VH in transgenic nonhuman in response to an antigen challenge by employing class switching. If applicants have evidence to support otherwise, applicants are invited to indicate page and line number for the written support for a method enabling the scope of claims set forth in claims 1, 3, 7-8, 10-11, 33-36, 39, 41 and 42 of the instant application. Therefore, the effective filing date for instant claims 1, 3, 7-8, 10-11, 33-36, 39, 41 and 42 is 04/24/2002.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered. In the instant case, applicants have cited multiple references in the specification but they have not been considered by the Examiner as no copy of any of the publication was provided.

Withdrawn-Claim Objections

The objection to claims 7-8 and 10-11 for reciting dependent claims as "a method according to claim.." are withdrawn in view of amendments to the claims.

Maintained-Claim Rejections - 35 USC § 112

Claims 1, 3, 7-8, 10-11, 33-36, 39 remain rejected under 35 U.S.C. 112, first paragraph, and newly added claims 41 and 42 are also rejected under 35 U.S.C. 112, first paragraph ,as failing to comply with the written description requirement.

As an initial matter, applicants' arguments pertaining to non functional CH1 domain is persuasive to the extent specification in view of prior art provide adequate guidance to one skilled in art to functionally eliminate CH1 to generate formation of single heavy chain antibody. Therefore applicant's argument pertaining to this issue is moot (see pages 10-11 of the arguments).

It is noted that applicants err in stating that claim 2 and 4 have been amended to recite the VHH exon comprises VHH coding sequence and VH exons comprises coding sequence that has been mutated. In fact, claims 2 and 4 have been canceled in the instant application. Examiner assumes that applicants meant amendments to claims 1 and 4 and not to claims 2 and 4.

Applicants' amendments to the claims have been fully considered but are not persuasive. In analyzing whether the written description requirement is met for the genus claim, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics, specific features and functional attributes that would distinguish different members of the claimed genus. The claims embrace producing single heavy chain antibody in a nonhuman mammal of any species expressing a VHH locus comprising a constant heavy chain gene when expressed does not express a functional CH1 domain.

The specification describes that a VHH or camelised VH single chain antibody does not possess a functional CH1 domain (see page 8, lines 27, page 9, line 10-15). The specification teaches that the transgenic mammal according to the present invention is smaller than a Camelid, preferably it is selected from the groups consisting of: a mouse, rat, guinea-pig, hamster, monkey and rabbit. Additionally, the specification discloses that a camelised VH exon/region may be a naturally occurring VH coding sequence derived from mammals other than Camelids or any homologue, derivative or fragment of the exon as long as the exon/region can recombine with a D region/exon, a J region/exon and a constant heavy chain region (see page 9, line 29-page 10). As amended, contrary to applicant's assertion claim 3 does not recite that the VH exons comprise coding sequences that have been mutated to be the same as a Camelid exon (see page 10, lines 8-9 of the applicants' arguments).

The specification is silent, however, on any homologue, derivative or fragment of an exon or a region that could recombine with a D, J region/exon that would produce the contemplated single heavy chain antibody in any nonhuman chimeric or transgenic animal. It is emphasized that neither the specification nor the prior art provide any details of transcript processing and the extent of the CH1 removal from the VHHDJ-Cg primary transcript. The state of art at the time of filing of this application was generally silent with respect to development of B-cells expressing VHH camelid antibodies and single chain heavy antibody in response to an antigen challenge.

The claims thus constitute a genus that encompasses plurality of hybrid loci comprising VH exons comprise coding sequences that have been mutated to be the same as a Camelid exon that would produce single heavy chain antibody in plurality of different chimeric or transgenic nonhuman mammal yet to be discovered, and since the specification does not discloses any single species of the VHH loci or VH exons comprising coding sequence that have been mutated that

may be capable of producing a single heavy chain antibody in any species of nonhuman mammal, the disclosed general structural features do not constitute a substantial portion of the claimed genus encompassing combination of hybrid loci with plurality of VH exons comprising coding sequence that have been mutated. As such, the Artisan of skill could not conclude that Applicant possessed any species. Hence, none of the claimed species could be demonstrated as possessed. see MPEP 2163.

Applicant must provide adequate description of such core structure and function related to that core structure of the VHH or VH loci such that the Artisan of skill could determine the desired effect could be achieved in the nonhuman mammal. Hence, the analysis above demonstrates that Applicant has not determined the core structure for full scope of the claimed genus of transgenic loci for contemplated biological activity in plurality of different nonhuman mammal. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. The breadth of the claims reads on producing single heavy chain antibody in any nonhuman mammal that express heterologous VHH loci or camelised VH exons comprising coding sequence that have been mutated. However, specification fails to provide any specific guidance on structure of any of the resulting transgenic hybrid loci that would produce single heavy chain antibody. It is known that the single heavy chain antibody require involvement of VHH germline gene in which the interface residues. The specification is silent with respect to the ineterface residues that are modified to produce single heavy chain antibody. Applicants have cited Janessens et al (Proc. National Academy of Science, 2006, 15130-15130, art of record) that disclose introducing Ig loci comprising two llama VHH region, all the human D and JH region, human C□, C□, C□2 and LCR in □MT transgenic mice that is capable of generating single chain antibody. However, it is noted that Janessens et al specifically used VHH locus (germ-line

VHHs) that were chosen with hydrophilic amino acid codons at positions 42, 50, and 52, one with and one without a hydrophilic amino acid at 49 that is identical to IGHV1S1. The specification fails to correlate specific elements of the VH loci that should be mutated resulting in formation of functional single heavy chain antibody in response to challenge to antigen. The claimed invention as a whole is not adequately described since claims read on plurality of different combination of hybrid loci comprising Vh exon that is mutated and specification fails to describe any species that would produce any functional single heavy chain antibody in any nonhuman mammal and which is not conventional in the art as of applicants effective filing date.

In view of the level of knowledge or skill in the art at the time of the invention, an Artisan of skill would not recognize from the disclosure that Applicant was in possession of the transgenic hybrid loci having different elements derived from different species of nonhuman mammal. The claimed invention as a whole is not adequately described if the claims require essential or critical elements or which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Thus, it is concluded that the written description requirement is not satisfied for the claimed genus.

The skilled artisan cannot envision the detailed chemical structure of the encompassed VHH or VH loci that comprises specific elements that are mutated to produce single heavy chain antibody in response to an antigen in any nonhuman mammal, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of

the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a method of producing single heavy chain antibody into any nonhuman mammal at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Maintained-Claim Rejections -35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 7-8, 10-11, 33-36, 39 remain rejected under 35 U.S.C. 112, first paragraph, and newly added claims 41 and 42 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants' arguments filed September 29, 2008 have been fully considered but are not persuasive. Applicants' argue that claims have been amended to recite transgenic mammal that by definition refers to germline transmission of the transgene and not somatic delivery (see page 12 of the argument).

In response, it is noted that contrary to applicants' argument none of the claim require nonhuman mammal whose genome comprises VHH heavy chain locus. In fact, as recited these claims merely require a non human mammal

expressing a heterologous VHH heavy chain locus specifically in B cell in response to the antigen challenge. It is emphasized that instant claims broadly read on VHH locus that is episomally maintained in a non human mammal. The specification has not provided working examples correlating to generating a single heavy chain antibody in response to any antigen in a mouse having claimed locus that is episomally maintained that generates heavy chain antibody by employing class switching. It is generally known in prior art that the generation of HCAbs in the camelid species also relies on the use of specific VHH genes which differ from VH genes used in the generation of conventional antibodies as they carry changes in some of the codons that encode the residues normally contacting the VL domain. The single heavy chain antibody requires involvement of VHH germline gene in which the interface residues are modified. It is emphasized that neither the specification nor the prior art provide any details of transcript processing and the extent of the CH1 removal from the VHHDJ-Cg primary transcript. This state of the prior and post filing art that shows several VHH and VH germline genes (see De Genst et al, Dev Comp Immunol. 2006; 30(1-2): 187-98, art of record page 192 and Riechmann et al J Immunol Methods. 1999; 231(1-2): 25-38, art of record). The state of art at the time of filing of this application was generally silent with respect to development of B-cells expressing VHH camelid antibodies and single chain heavy antibody in response to an antigen challenge (De Genst et al, Dev Comp Immunol. 2006; 30(1-2): 187-98, art of record). As stated in previous office action earlier work in the filed showed functional human VH domains that could be selected from randomized phage display libraries and that rearranged heavy chain genes engineered to be devoid of CH1 domain can be expressed (see Riechmann et al J Immunol Methods. 1999; 231(1-2): 25-38, art of record and Sitia et al Cell. 1990 Mar 9; 60(5):781-90, art of record). Applicants have extensively relied on a post filing art of Janessens et al (Proc. National Academy of Science, 2006, 15130-15130, art of record) for enabling support that uses specific elements in the VHH locus

(germ-line VHHs) that were chosen with hydrophilic amino acid codons at positions 42, 50, and 52, one with and one without a hydrophilic amino acid at 49 that is identical to IGHV1S1. The enabling embodiments further describe a method that discloses introduction of frt and lox P sites 5′ to the Cμ switch region, and a second lox P site placed 5′ to the Cγ2 switch region, resulting in MGS or MGΔ. The specification fails to recognize the specific elements of VHH locus or plurality of different combination of constant heavy chain regions of different species that are disclosed by Janessens et al. MPEP 2164.05(a) [R-2] states "[T]he state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1325-26 (Fed. Cir. 2004) ("a patent document cannot enable technology that arises after the date of application"). Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. *In re Gunn*, 537 F.2d 1123, 1128, 190 USPQ 402,405-06 (CCPA 1976); *In re Budnick*, 537 F.2d 535, 538, 190 USPQ 422, 424 (CCPA 1976). While a later dated publication cannot supplement an insufficient disclosure in a prior dated application to make it enabling, applicant can offer the testimony of an expert based on the publication as evidence of the level of skill in the art at the time the application was filed. *Gould v. Quigg*, 822 F.2d 1074, 1077, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987). In the instant case, the specific elements disclosed by the Janessens et al (VHH germ line gene GenBank accession no. AF305944 and specific combination of constant regions) are not disclosed in the specification in same manner as it has been described in Janessens et al for making transgenic mouse. Hence, the nature of the invention is not reasonably predictable for any of the numerous possible coding sequences of VHH or VH exon comprising VH coding sequence that are mutated to be the same as Camelid exon as claimed, due to the unpredictability of structure-function relationships. Moreover, given the lack of

reasonable predictability between structure and function, the identification and subsequent analysis for genus of such identified or yet to be identified variant to produce single heavy chain antibody would require further and undue experimentation. Furthermore, the expert testimony based on the publication has been primarily used to rebut the other issue of enablement rejection. It is noted that Applicants were previously requested to indicate the support for the specific construct in the specification that includes specific elements that were relied for the enabling support (see page 23, para. 1 of the office action). An artisan would have to perform undue experimentation to make and use the invention without reasonable expectation of success.

Applicant argues that they need not disclose and enable every potential method of making and using; Applicant, rather, must enable making and using in all non-human transgenic mammals. Applicant has done so. See the Declaration of Dr. Grosschedl, paragraphs 13-15 and 17. Applicants assert that the transgenic made by Janssens using the mouse could be applied to the other species of mammal such as goat, rat, rabbit and pig. Applicants assert that introduction of the transgene into germline of nonhuman mammalian system was well established at the time of application.

In response, it is true that applicants need not disclose and enable every potential method of making and using the claimed method. However, Applicant should note that "case law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970. It is noted that the Grosschedl declaration is not commensurate with the scope of the claimed invention as the declaration relies on the teaching of Janssens. It is noted that specification do not disclose the specific elements of two llama VHHs that are introduced having characteristic amino acids at positions 42, 49, 50, and 52, while VHH2 had a Q instead of an E at 49. In the instant case, neither expert testimony

nor specification disclose, or enable one of skill to make, a construct containing the essential nucleotide sequences in germline configuration necessary for class switching to occur. Please note that at the time the claimed invention was made, applicants did not have in their possession of specific modification set forth in VHH1 or VHH2 as disclosed in Janssens in germline configuration capable of undergoing class switching to generate a single heavy chain antibody. It is emphasized that the issue is not how to make transgenic non human animal by pronuclear injection or whether other nonhuman mammal or a progeny thereof could be produced using same method. The breadth of the invention embraces expressing chimeric loci comprising VHH, at least one Cμ constant heavy chain gene and at least one of Cγ, Cα, Cε, or Cδ constant heavy chain gene which when expressed does not express functional CH1 domains. It is emphasized that specification contemplated this may occur by mutation, deletion substituted or other treatment of the CH1 and CH4 exons of the constant heavy region gene(see page 11, line 31-32 to page 12 lines 1-2). Thus, in spit of prior disclosure of constant heavy chain region, when expressed does not express a functional CH1 domain, specification fails to provide any details of transcript processing and the extent of the CH1 removal from the VHHDJ-Cg primary transcript. As stated in previous office action, in post filing art, Janessens et al (Proc. National Academy of Science, 2006, 15130-15130, art of record) disclose Ig loci with two llama VHH region, all the human D and JH region, human Cμ, Cδ, C γ2 and LCR introduced in μMT transgenic mice still show the presence of CH1 exon which was spliced out and no chimeric Ig expression (figure 7). Janessens et al emphasize that lack of CH1 is crucial for HCAb secretion, but the camelid splice mutation at the 3' CH1 border is insufficient for CH1 removal, thus more than this point mutation is required (see page 15134, col. 1, para.2). Thus, the teaching provided in the specification is generic and required further experimentation to determine the transcript processing and the extent of the CH1 removal from the VHHDJ-Cg primary

transcript. Additionally, the single heavy chain antibody require involvement of VHH germline gene in which the interface residues are modified and the availability of the HCAb-specific CH (Cg) gene. It is emphasized that neither specification nor prior art provide VHH germline gene in which the interface residues are modified to produce a single heavy chain antibody in a transgenic non human mammal. The state of the art of the VHH loci, and the breadth of the claims, it would have required undue experimentation at to the time of filing to make and/or use the invention as claimed.

With respect to applicants' argument of use of animal as bioreactor and missing citation on page 26 of previous office action, it is noted that the same citation is also presented on page 18 of the office action. Applicants' assertion that the cited reference is misplaced in not fully persuasive because, prior art recognizes the inefficiency of pronuclear microinjection transgenic techniques and the unpredictability of transgene expression when applied to generating transgenic cows, goats and sheep, for example (see page 6, paragr. 1, line 1 to page 7, line 4, Keefer Animal Reproduction Science 82-83: 5-12, 2004). The reference is applied to the extent post filing art of Janessens et al reported the difference in results from those obtained by Zou et al with respect to the role of LC rearrangement (J Immunol, 2005, 175:*3769–3779)* to level of expression of the locus (and, thus, signaling). Janssens et al attributes this difference in results to use of LCR in the constructs (see page 15134, col.2, para.1). Applicants' amendments to the claims reciting LCR providing the expression of VHH heavy chain overcomes the rejection pertaining to this issue. Therefore, applicants' arguments to this issue are moot. Examiner also acknowledges correct spelling of Dr. Grosschedl, which was inadvertently misspelled in previous office action.

Applicants also argue that quantifiable titer is not required. Applicants also cite the declaration of Dr. Weiner and cite the reference of Ward to suggest that amplification technology was known to one of ordinary skill in the art (see page 15

of the argument). Applicants also argue that endogenous locus should not interfere with transgene expression because allelic exclusion will ensure that some cell will express the transgene.

In response, Examiner would agree that instant claims do not require quantifiable titer. It was indicated that disclosed transgenic loci taught by Janssens et al could be express transgene in some cells because allelic exclusion, however, the issue is not whether transgenic loci could be expressed in B cells of wild type animal rather issue is whether single heavy chain antibody could be produced in any nonhuman mammal in response to antigen challenge to make use of the invention. It was indicated that the expression of single heavy chain antibody on reduced western blot gel does not provide enabling support to one of skilled in the art that contemplated antibody could be produced in any wild type chimeric nonhuman mammal to make use of any such antibody irrespective of titer. The specification does not provide any guidance to characterize any resulting single heavy chain antibody in response to antigen challenge.

Additionally, as stated before, applicants are relying for a post-filing art in support of enablement. Applicants' argument and declaration by Drs. Louis M. Weiner and Grosveld are not commensurate with full scope of the claim. In the instant case, contrary to applicant's arguments claims are not limited to any specific loci of VHH expressed in any transgenic mouse whose genome comprises VHH loci of the invention, rather it embraces producing single heavy chain antibody in any nonhuman mammal that express any heterologous VHH loci or any camelised VH loci that comprises at least one constant heavy chain when expressed does not express a functional CH1 domain that may occur by mutation, deletion substituted or other treatment of the CH1 exons of the constant heavy region gene (see page 11 of the specification). As stated before the single heavy chain antibody require involvement of VHH germline gene in which the interface residues are modified and the availability of the HCAb-specific CH (Cg) gene. It is emphasized that neither

specification nor prior art provide any details of transcript processing and the extent of the CH1 removal from the VHHDJ-Cg primary transcript. Applicants have extensively relied on a post filing art of Janessens et al (Proc. National Academy of Science, 2006, 15130-15130, art of record) for enabling support that uses specific elements in the VHH locus (germ-line VHHs) that were chosen with hydrophilic amino acid codons at positions 42, 50, and 52, one with and one without a hydrophilic amino acid at 49 that is identical to IGHV1S1. The specification fails to provide structure of transgenic loci that require specific modification set forth in VHH1 or VHH2 as disclosed in Janssens in germline configuration capable of undergoing class switching to generate a single heavy chain antibody.

Conclusion

No claims allowed

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Lonberg et al (US Patent No. 5569825, dated 10/29/1996, art of record).

Green et al (20030093820, dated 11/30/2001, art of record)

Riechmann et al (J Immunol Methods. 1999; 231(1-2): 25-38, art of record).

Imam et al (2000) *Nucleic Acids Res* 15, E65.

Nguyen, et al (1999) Mol Immunol 36, 515–524.

Nguyen et al (2000) *EMBO J* 19, 921–930.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory

action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anoop Singh
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/Valarie Bertoglio/
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